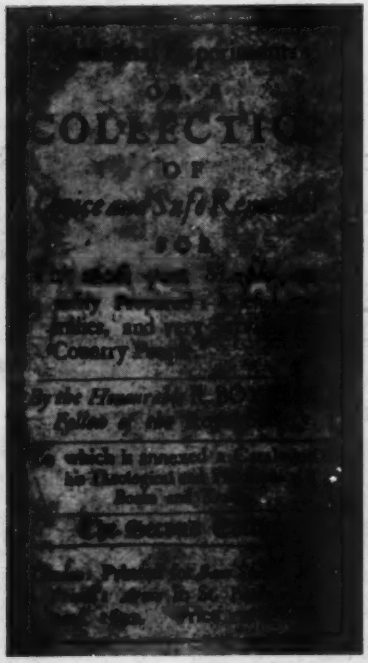
AMERICAN JOURNAL OF PHARMACY

and

THE SCIENCES SUPPORTING PUBLIC HEALTH

SINCE 1825



Title Page of "Medicinal Experiments or a Collection of Choice and Safe Remedies", by the Honorable Robert Boyle. (See page 48.)

FEBRUARY
1943

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The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

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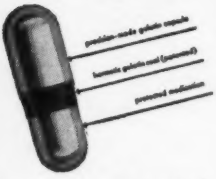

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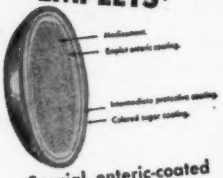

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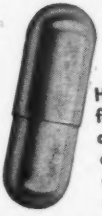

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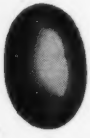

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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CONTENTS

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OUR COVER

THE Library of the Philadelphia College of Pharmacy and Science, through the friendly generosity of an alumnus, H. B. Weaver, Burlington, New Jersey, Class of 1881, recently acquisitioned a copy of the early printed work of the Honorable R. Boyle, printed in London in 1692.

It is entitled "Medicinal Experiments or a Collection of Choice and Safe Remedies." This is the same Robert Boyle whose name is associated with certain physical laws having to do with properties of gases. (The cover carries a photostatic copy of the title page.)

The context of the book is extremely interesting, and while the formulas are for the most part simple and easily prepared, many of them have been discarded into the limbo of forgotten things—many remedies containing vegetable drugs which might perhaps well be reconsidered even in this day and generation when we place so much reliance on the synthetics.

There are many unusual combinations which are a far cry from today's sterile products—thus:

Recipe 156: "An Experienc'd Magnetical Cure of the Yellow Jaundies. Take the Gall-Bladder of a Sheep, and near the top, without emptying the Liquor, make a small hole, at which put in two or three drops of the Patient's warm Urine; then tye up the upper part of the Bladder, and hang it in the free Air till it dry up."

Of much interest too to those who love old books and old sentiments is the original owner's inscription written in long hand on the inside of the front cover, and this is the inscription:

Martha Broomhead is my Name;
Old England is my Nation;
Ossett is my Dwelling-place,*
And Christ is my Salvation.

*Ossett is a village in the West Riding of Yorkshire between Leeds and Wakefield.

EDITORIAL

A PHARMACEUTICAL TRAGEDY

SEVERAL years ago there lived a pharmacist who, the son of a pharmacist, was known the county over as an outstanding example of professional integrity and skill. His pharmacy was the ultimate in cleanliness, order and real professional service. Pharmacy was his life's work and his name on a label gave both product and prescription a guarantee that indeed money could not buy.

There came a day, however, when this pharmacist came to the end of earthly service and his establishment as one of his assets passed to his estate. It now became simply a means of satisfying the desires of his heirs and everything was subjugated to this end. The policy of service to physicians and the community now was ended. Bigger and better profits was the code of management. In order to squeeze the last drop of return, low grade help was employed, the store became progressively dirtier until a cheap restaurant was clean by comparison. The quiet professional atmosphere of the past was replaced with the raucous cries of schoolboys who now made it their "hang-out." Biologicals were no longer refrigerated, inferior brands replaced those of ethical houses and for long periods during the day no pharmacist was even in charge. Still the name whose bearer labored so long for pharmacy graced the front while he lay coldly silent and, we hope, oblivious to its disgrace.

Why is it that amongst all the professions only pharmacy permits this evil? Can one imagine a famous physician having his practice exploited after his death by interests motivated solely by profit. When a physician dies so does his empire or else he is succeeded by another who is not directed and controlled by an estate. This evil in pharmacy is monstrous since public confidence and public welfare is betrayed by such a system. If justice is to be done to all, might it not be better for a pharmacy, upon the death of its owner, to be operated by the State Board of Pharmacy or other responsible group until a suitable purchaser could be found and at a

fair price. Non-professional ownership is, generally speaking, inimical to the public welfare, since without professional training the responsibilities of operating a pharmacy cannot be appreciated fully by a layman. A pharmacist-manager invariably is confronted with situations wherein professional conduct and commercial expediency are in conflict and pressure from ownership is often greater than he can be expected to resist.

Those who object to any such argument are firmly entrenched and "Unfair!" or "Unconstitutional!" will be their comment. But even this is an empty phrase if pharmacists universally would endorse this plan and act accordingly. The very existence of non-pharmacist owned stores depends upon pharmacists. We have but to act unanimously and they close or else convert themselves into luncheonettes or notion stores. It is only with our names and certificates that they capture the prestige that only real pharmacy deserves; a prestige that properly belongs to the individual and not to a group of inanimate drugs and fixtures.

Either pharmacists must by their every act and deed give evidence of their belief in pharmacy as a profession and stick together toward this end or the day will come when their "business" will be in other hands and their own services will command both little respect and small reward. We are the masters of our destiny! What shall it be?

L. F. Tice

THE METABOLISM AND TOXICOLOGY OF ETHYLENE GLYCOL AND ETHYLENE GLYCOL DIACETATE

By Michael G. Mulinos, Leo Pomerantz and Mary E. Lojkin

IN a chemical sense the di-hydric alcohols and their derivatives have been designated by the generic name of *Glycols*. These substances have certain chemical and physical properties in common which have led to a variety of commercial uses. Used as solvents for lacquers they may be inhaled and absorbed resulting in irritative and remote toxic manifestations. Used as solvents for flavoring agents and medicinals (1) they may be imbibed in sufficient quantities to result in gastritis, and after absorption, to specific lesions of the internal organs.

The name *Glycol* for this group of substances does not distinguish sharply among the various derivatives. Toxicologically, the glycols may be divided into 2 main classes: (a) the *simple glycols* such as ethylene and propylene, and their esters; and (b) the *glycol ethers* such as dioxane and diglycol, as well as other derivatives. This distinction has been emphasized by Kesten et al. (2, 3) who have found that the typical hydropic degeneration of the kidney tubules is found only after toxic doses of the glycol ethers best represented by dioxane.

The most extensive "single dosage" investigation on the toxicity of ethylene glycol (E. G.) was that reported by Laug et al. (4). Using statistical methods and a unit of 10 animals for each dose of E. G. tried, and death as the criterion of toxicity (MLD), they came to the conclusion that 5 cc. per kilo of rat was the MLD 50. In contrast, similar experimental procedures used by Smyth et al. (5) resulted in an MLD 50 of E. G. of 8.54 Gm. and for E. G. diacetate of 6.86 Gm. per kgm. of rat. Huddleston (6) found that E. G. poisoning in dogs resulted in bradycardia which was sometimes preceded by tachycardia. Both puppies and adult dogs developed sino-auricular block, while in the adult dogs there were also nodal and ventricular

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extra systoles. From larger doses, Hanzlik et al. (7) obtained fatal convulsions from an intravenous infusion of 20 cc. of E. G. per kilo. By mouth, 2 doses of 2 cc. per kilo caused ataxia with recovery while in another dog a single dose of 2 cc. per kilo resulted in convulsions with death. There is a marked discrepancy in the effective dose levels as reported by these authors. Apparently, convulsions from fatal doses do not occur in mice, rats, guinea pigs, or rabbits (3, 4). Busquet (8) concluded that the convulsant action of E. G. on the frog was upon the striated muscle, peripheral to curare and independent of the central nervous system.

In vitro, Bernheim and Handler (9) have shown that E. G. is oxidized to aldehyde by liver preparations. Ethylene glycol is in part oxidized into oxalic acid (10). Hunt (11) believed (but without due proof) that the toxic action of E. G. was due not to the drug itself, but to the production from it of toxic amounts of oxalic acid. Wiley et al. (12) on the other hand, found that dogs given 5 cc. or 8.5 cc. per day for seven days gave no symptoms. Less than 0.5 per cent. was excreted in the urine as oxalate. They concluded that the conversion of E. G. to oxalate was not sufficiently extensive to account for the toxicity of E. G. Chiray et al. (13) from feeding experiments on rats, also found that only about half of one per cent. of ingested E. G. is excreted as oxalate in the urine and concluded that ". . . there is no extensive production of oxalic acid from the precursors."

Page (14) could obtain no gluconeogenesis in diabetic dogs and Newman et al. (15) determined that E. G. depressed the oxygen consumption and increased the lactic acid formation of the perfused liver. Hanzlik et al. (7) found that E. G. decreased the glycogen content of the liver. Therefore, Franck (16) seems not to be justified in his advice that E. G. be used as a food and as a substitute for ethyl alcohol.

The present report deals with the metabolism and toxicity of ethylene glycol, $HOCH_2CH_2OH$, and the diacetate ester of ethylene glycol, $CH_3COOCH_2CH_2—OCOCH_3$ (E. G. Diac.). Experimental data upon animals and accidental ingestion by human beings indicate that E. G. has a low toxicity and that its use in industry does not constitute an undue hazard to health. Nevertheleess, its toxicity is too high to recommend it as a medicinal vehicle.

Our toxicological studies fall into two classes: (a) *Acute toxicity* resulting from a single large dose or from a number of divided doses

given within 12 hours, and yielding what is commonly designated as the minimal lethal dose (MLD); and (b) the *Chronic toxicity* which results from the daily or the more occasional administration of sub-lethal doses, leading to the development of symptoms due to the frequent repetition (accumulation) of the injury resulting from the drug.

Our researches are in accord with the data reported in the literature, in that E. G. exerts its *acute toxicity* as a non-specific phenomenon of over-dosage due to hypertonicity, to irritation, to hemolysis and to a fall in the blood pressure resembling shock, especially when it is given intravenously. The *chronic* effects are due in great part to the partial oxidation of the E. G. to oxalic acid and its deposition in the kidney tubules as calcium oxalate casts. The same is true for the ethylene glycol diacetate.

Experimental

The experiments were performed upon rats and rabbits. Rats were used for the long-time feeding experiments while the intravenous injections were given to rabbits.

The *acute toxicity* experiments were performed on rabbits by injecting the E. G. intravenously, usually in the pure form (Sp. Gr. 1.1155). In rats the glycol was given by stomach tube, according to the procedure of Laug et al. (4).

The *chronic toxicity* experiments were carried on using rats and administering the ethylene glycol in the drinking water as 1 or 3 per cent. solutions, and the ethylene glycol diacetate as 1, 3 or 5 per cent. solutions. Twenty-one young rats (4 groups) from 33 to 55 days of age were put on a one per cent. E. G. solution in order to determine the effect upon growth. All experiments were controlled by being run in parallel with rats fed water, glycerine or propylene-glycol solution. As a test for the sensitivity of rats and rabbits to oxalate, rats were fed a 1 or 2 per cent. solution of sodium oxalate, and rabbits were injected intravenously with sodium oxalate. Finally, experiments were performed to determine the chemical nature of the crystalline deposits in the kidneys and with the quantitative determination of oxalate in certain kidneys.

Results

Acute Toxicity Experiments: Thirteen rabbits received from 1 to 4 cc. of pure E. G. per kilo intravenously. They were then sac-

rificed in from 24 hours to 2 months after the injection depending upon symptoms or a predetermined schedule.

Following the injections, all the rabbits showed either an obviously bloody urine or a positive benzidine test for occult blood. Crystals of calcium oxalate occurred in the convoluted tubules of 3 rabbits, two of which had received 2.5 cc. and one, 4 cc. of E. G. per kilo. Their urine was also positive for albumin terminally (20 hours to 10 days after the injection). The NPN of the blood was elevated, the highest being 226 mgm. per cent. (normal is 43) 8 days after the injection. The kidneys were large, the pair weighing from 17 to 22 Gm. (normal 10 to 14 Gm.). Two rabbits which were injected with 4 cc. per kilo died within 48 hours and showed no pathological changes. Two rabbits survived 1 cc. per kilo and 6 survived 2 cc. per kilo. Of these, one showed a persistent trace of albumin and another a transient rise in NPN to 112 mgm. per cent. One rabbit received 1 cc. per kilo as 50 per cent. solution for 2 days and 0.5 cc. on the third day. At this time the hemoglobin concentration of the blood had fallen from 80 per cent. before the injections to 55 per cent. (probably due to hemolysis). Ten days after the last injection the left kidney was removed at operation and weighed 13 Gm. or about twice the normal. Microscopic examination revealed crystalline masses in several convoluted tubules with dilatation proximally. The rabbit was allowed to survive for 2 months when it was autopsied. The blood NPN had risen steadily from the normal of 44 mgm. per cent. to 91 mgm. per cent. on the day before the operation. Thence the NPN fell gradually to 56 mgm. per cent. at autopsy. The right kidney weighed 12.5 Gm. and was pitted with scarified areas. The cortex was pale. The bladder urine contained 3 plus albumin and an occasional cast. Microscopic section revealed cortical linear scars and rare granular brownish casts in convoluted tubules. This experiment indicates that healing with return of function followed the injury induced by the injections of E. G. In none of the rabbits was there any evidence of vacuolization of the kidney or liver suggestive of hydropic degeneration.

Five rats weighing approximately 200 Gm. each were given by stomach tube E. G. 5 cc. per kilo, the dose reported as MLD 50 by Laug et al. (4). All 5 rats became ataxic, depressed and then moribund as if anesthetized, but the less affected ones would respond to a moderate tail pinch. The rats were autopsied when in our opinion

they were near death in order to eliminate the chance that any kidney lesions were masked by post-mortem changes. Two were autopsied within 8 hours of the administration, one in 10 hours, one in 14 hours while the fifth one recovered completely. Examination of the kidneys revealed no abnormality grossly either in appearance or in weight. On microscopic examination there was slight fraying of the convoluted tubules with some flattening of the epithelium and widening of the lumina. There were no crystalline deposits and no evidence of the type of hydropic degeneration which occurs with dioxane (17). Our findings for E. G. do not agree with those of Laug in which he found ". . . in nearly all cases hydropic degeneration of the cells lining the cortical convoluted tubules . . ." However, since the published photomicrograph resembles the type of lesion found by ourselves, complicated by some post-mortem autolysis, the discrepancy may be one of terminology. (See also 18.) Certainly, the type of *hydropic degeneration* which occurs with the various glycol ethers does not occur with ethylene glycol (2, 3, 17, 19). For the sake of consistency, therefore, it is suggested that the term hydropic degeneration be reserved for the specific type of lesion implied by the term, namely: "The most marked change was seen in the secretory tubules of the cortex. Their lumina were completely occluded by outlines of swollen cells, from which all trace of nucleus and cytoplasmic stain had disappeared leaving clear intracellular spaces. These faintly outlined cell membranes were in turn surrounded by the tubular basement membrane. These intracellular spaces were devoid of fat or glycogen and their ballooned appearance suggested a fluid content which remained unstained. This dissolution of cytoplasm stopped short at the boundary zones, the epithelium of the collecting tubules being normal" (17). Acutely toxic doses of E. G., and as will be seen presently, chronically toxic doses, do not produce this type of lesion.

Chronic Toxicity Experiments: In this study, groups of 5 hooded rats were used as the experimental unit, segregated as to sex except when the influence upon procreation was being studied. The glycol was administered in the drinking water and the amount of fluid taken was measured daily. The group was weighed once each week. The experiment was run indefinitely or until the animals sickened, when they were autopsied under ether anesthesia.

The pathological results from the drinking of ethylene glycol have been reported previously (3). One per cent. E. G. solution

is taken by each rat to the amount of approximately 25 to 30 cc. per day. Of 24 adult rats who took the solution for from 8 to 79 days, 17 showed crystalline deposits in the convoluted tubules. None showed any evidence of "hydropic degeneration" of the tubules. The variability of response to the feeding of dilute E. G. solutions is well illustrated by the fact that a rat receiving a one per cent. solution died in 8 days with the tubules definitely streaked with crystals, while other rats drank the solution for 79 days; they developed normally and at autopsy showed no kidney pathology. When the tubules of the kidneys contain crystals, the NPN content of the blood is likely to be elevated, presumably due to tubular obstruction. The NPN of normal rats used in our control series and which had been kept on water or had been given glycerine or propylene glycol in the drinking water, ranged from 30 to 60 mgm. per cent. Somewhat higher figures than these obtain in animals which have no obvious pathological lesions of the kidneys but which have become dehydrated terminally. Thus in experiments with acute starvation, it is not unusual to obtain NPN readings of as high as 90 mgm. per cent. Therefore, in the present and subsequent series where the animals may sicken to the point of death, or starve voluntarily rather than drink the solution offered, the NPN figures of 90 mgm. per cent. should not be interpreted as indicative of renal damage. The highest NPN due to E. G. recorded by us in rats was 167 mgm. per cent. while most of the figures were below 100. Since the majority of the rats which showed crystalline deposits in their kidneys died or sickened to the point of death, but showed relatively low NPN values, we are of the opinion that the cause of death in these animals must have been due primarily to other than renal causes, such as starvation and calcium deprivation. That the latter may be important in this case is suggested by the experiments of Kohman (20) in which spinach was added to a calcium-low diet. Due to the fact that spinach contains oxalates to about 10 per cent. on a dry weight basis their animals had a high percentage of death with bones low in calcium and reproduction did not occur (probably due to the inanition (21)). Considerable spinach oxalates appeared in the urine, showing that the oxalates were absorbed from the alimentary tract of the rat. On the other hand, large amounts of oxalates fed by us did not result in the death of the rats, so that marked deprivation of calcium was not contributory to the lethal damage. Dunn, Haworth and Jones (22, 23) found that in experimental oxalate nephritis in rabbits there is a marked retention

of urea in the blood which may last for a month from larger doses. In the type of nephritis seen after the prolonged administration of E. G. to the rat, the NPN is relatively low, so that one is led to the conclusion that the rat kidney is not affected by oxalates in the same way as in that of the rabbit.

Of 21 baby rats between 33 and 55 Gm. in weight who received one per cent. E. G. in the drinking water during their subsequent growth period, 11 lived for 77 days when they were autopsied. Of these, only 4, all in one group, grew normally as compared with water fed controls. These weighed 184 Gm. after 9 weeks on the E. G. It is concluded that the E. G. markedly depressed the rate of growth of young rats, the mortality being almost 50 per cent. within 9 to 11 weeks of the institution of the experiment. However, the data show that young rats are no more susceptible than adults to the chronic effects of E. G.

Experiments with sodium oxalate: Rats of both sexes were given in their drinking water 1 or 2 per cent. sodium oxalate as the sole source of fluid. Five young rats which averaged 86 grams received one per cent. oxalate for 103 days, during which time they gained in weight to an average of 220 grams. During this time they bore 3 litters of normal young. On the 103rd day, two of the rats were sacrificed for routine study and proved to be entirely normal. The remaining 3 rats were changed to a 2 per cent. solution of oxalate for an additional 113 days. One of the 3 died on the 201st day and was negative microscopically. These rats had been taking the oxalate solution for 216 days, during which time each had received 75 grams of sodium oxalate. At autopsy the tissues were negative, showing that these doses of sodium oxalate did not harm the kidneys nor did they lead to oxalate urinary lithiasis.

A second set of 5 young rats was studied using 2 per cent. in the drinking water from the outset. These rats average 78 grams in body weight at the beginning of the experiment and after 108 days when the experiment was terminated, they weighed 150 grams as compared with 220 grams for rats that had been on one per cent. solution for an equal length of time. Each of these rats ingested 54 grams of sodium oxalate during the 108 days of the experiment, or about 3.3 grams per kilo per day, with no obvious symptoms of osteoporosis or of rickets. On the 48th day there was born a litter of 6 young which appeared normal but which were taken away from the mother.

At autopsy, the stomachs were full of food and there was no evidence of inflammation. The NPN was normal and varied from 48 to 63 mgm. per cent. The kidneys were negative and weighed from 1.05 to 1.45 grams; microscopic examination revealed apparently normal kidneys. One female rat showed an early pregnancy. Except for the lack of normal body growth, the cause of which was not obvious, these rats appeared unaffected by this regime.

Six rabbits were injected intravenously with a one per cent. solution of sodium oxalate in physiological salt solution. The minimum lethal dose proved to be 60 mgm. per kilo given as a single dose. The NPN was raised and the urine contained oxalate crystals and albumin. The kidneys were large and congested. When the dose of 60 mgm. per kilo of oxalate was administered in 2 daily doses of 30 mgm. each, death did not follow although there was obvious injury to the kidneys as shown by albuminuria, a rise in the NPN, and an increase in size of the kidneys at autopsy. One rabbit survived the daily injection of 15 mgm. of sodium oxalate for 17 days during which time 195 mgm. of sodium oxalate had been administered. The animal gained in weight during this time. Autopsy revealed slightly enlarged kidneys (17 Gm.) but the NPN was 40 mgm. per cent. Another animal survived daily injections of sodium oxalate of from 10 to 30 mgm. per day in increasing dosage until a total of 380 mgm. per kilo had been administered in thirty-seven days. This animal gained in weight from 2.1 to 2.5 kgm. and at the end of this time the NPN was 48 mgm. per cent.

These experiments demonstrate that sodium oxalate given in doses representing over 10 per cent. of the toxic doses of E. G. is not fatally toxic. It is concluded that the acutely toxic effects of E. G. given intravenously are not due to the oxalates produced from the oxidation of the E. G., but to other causes. Chronically toxic doses of E. G. end fatally due to calcium oxalate nephritis (obstructive) while acutely toxic doses cause death which can be but partly ascribed to the kidney.

The conversion of E. G. to oxalic acid has been deduced from the fact that after the administration of E. G. there was an increase in the oxalate content of the urine (24 to 29). Morris et al. (30) described renal calculi and nephritis after large doses of E. G. Hanzlik et al. (29) show a photomicrograph of a kidney containing what was claimed to be calcium oxalate crystals from a rat which had been fed

E. G. Kesten et al. (3) described analogous crystals which occurred in the majority of rats which had been given one per cent. E. G. in the drinking water as being calcium oxalate because the material reduced silver salts and gave very high readings for calcium by analysis. However, it is well known that injured kidneys deposit calcium salts, usually as phosphate, sulfates or carbonates; accordingly an investigation was instituted to fix more satisfactorily the identity and the quantity of the calcium salts which are deposited under these conditions.

The kidneys of the rats ill after the ingestion of E. G. were ground with sand and digested with 3M HCl. The hot filtrate was neutralized with ammonium hydroxide, and the precipitate was filtered and re-dissolved with hot HCl and re-precipitated with ammonium hydroxide at pH 6.9. Microscopic examination of the precipitate revealed a crystalline shape similar to that ascribed to calcium oxalate by Chamot and Mason (31). When the hot hydrochloric acid solution was treated with an excess of barium chloride, the subsequent crystalline precipitate corresponded to the crystalline configuration of barium oxalate. Qualitative tests for phosphate and sulfate were negative. One aliquot of a hot acidified solution of the crystals was titrated with potassium permanganate. Another aliquot was treated with an excess of oxalic acid and the precipitate was eventually weighed both as calcium carbonate and calcium oxide. The figure for calcium corresponded quantitatively with the figure obtained after the original titration with potassium permanganate, indicating the identity of the original precipitate as calcium oxalate.

Thirteen rats were given 3 per cent. of E. G. in the drinking water in order to determine quantitatively the amount of calcium oxalate which is deposited in their kidneys. The essential features of the experiment are given in the table. The oxalate content of the kidneys was compared with the liver and also with the tissues of those rats which had been kept on pure water. Again these figures show in a quantitative manner that mere deposition of calcium oxalate in the renal tubules plays no important part in the early death of these animals. There appears to be no correlation between the amount of E. G. taken and the amount of oxalate deposited. Some rats succumb early, while others, such as rat 9, drank one per cent. E. G. for 221 days and showed only 2 mgm. of oxalate deposit. The fact that 3 per cent. E. G. is more quickly toxic than 1 per cent., suggests a possible explanation for the individual susceptibility of various rats. The total

QUANTITATIVE ESTIMATION OF OXALATE IN KIDNEYS AND LIVER OF RATS GIVEN ETHYLENE GLYCOL IN THE DRINKING WATER

Exp. No.	Sex	Procedure: Ethylene Glycol in drinking fluid	Duration of Experiment days	Condition at autopsy	Oxalate Crystals: In Kidney, Grossly	Oxalate Crystals: In Kidney, mgm. per 100 gm. of tissues	Oxalate Crystals: In Liver, mgm. per 100 gm. of tissues
1	female	3 per cent.	5	coma	none	150	—
	female	3 per cent.	7	coma	none	150	—
2	male	3 per cent.	7	died	none	540	—
3	male	3 per cent. for 7 days, then 1 per cent.	51	ataxic	pos.	600	—
	male	1 per cent.	62	died	pos.	600	—
4	male	3 per cent. for 7 days, then 1 per cent.	64	died	pos.	1,380	—
	male	3 per cent.	7	died	none	1,380	—
5	male	1 per cent.	123	died	pos.	2,650	—
6	female	1 per cent.	201	coma	none	330	3
7	female	1 per cent.	206	died	none	370	2
8	female	1 per cent.	207	ataxic	pelvic lithiasis	880	2
9	female	1 per cent.	221	ataxic	pos.	2,740	2
10	female	1 per cent.	221	ataxic	none	100	1
11	female	1 per cent.	237	coma	pos.	540	—
12	female	5 control rats	237	excellent	none	2	1

daily dose is not a sure index of impending toxicity, but rather the amount of drug that is taken at any one time. A rat which drinks his 25 cc. per day in a few large draughts is more likely to be affected than is the one which drinks just a few drops at a time throughout the day. In the latter, the concentration of drug in the blood remains below toxic levels.

Ethylene glycol diacetate (*E. G. diacetate*) is easily hydrolyzed to E. G. and acetic acid so that its toxicity may be expected to be somewhat like that of E. G. itself, as reported by Kesten et al. (3). Lepkovsky (32) fed the ethyl esters of E. G. to rats by putting 25 to 60 parts per 100 parts of diet. After 40 days the kidneys were reported to be enlarged, heavier than normal and "milky white" in color or mottled with white and the surface studded with nodules and pits. From the description it is assumed that there was no difference between these kidneys and those of animals fed the esters of diethylene glycol. Wiley et al. (12) reported oxalate formation from ethylene glycol monoacetate.

Ten 150 gram female rats were given 5 per cent. E. G. diacetate in the drinking water. They drank an amount of the solution to within 20 per cent. of that taken during the control period and soon became ill and ate less than before. One rat died after a week while the last rat was killed after 37 days because of impending death; weight 106 grams. There were crystals in the kidneys of the rat that died after having been on the solution for one week. The identity of the crystals was proved chemically to be calcium oxalate and indistinguishable from those obtained with E. G. alone. The NPN content of the blood was determined only on the 2 rats which did not die, being 200 mgm. per cent. (15 days) and 218 mgm. per cent. (37 days) indicating definite kidney damage.

Five male rats were given one per cent. E. G. diacetate as the sole source of drinking water for 110 days during which time they grew normally and showed no gross effects from the drug. On the 111th day the solution concentration was increased to 3 per cent. for 20 days, and the rats were killed and the kidneys analyzed for calcium content (3). The NPN was found to be from 47 to 76 mgm. per cent. The kidneys of 3 of the rats were markedly enlarged (2.5; 2.2 and 2.6 grams each) and the pale surface was mottled with masses of crystals which extended deep into the cortex. One of these kidneys contains 819 mgm. of calcium per 100 grams of kidney.

Summary

A. Experiments were run upon rabbits and rats in order to determine the toxicity of ethylene glycol and of ethylene glycol diacetate.

1. The identity of the crystalline deposits ocurring in the tubules of the animals was determined by several methods. Quantitative estimations of the calcium and of the oxalate were made.
2. Sublethal doses of ethylene glycol injected intravenously into rabbits resulted in a deposition of calcium oxalate crystals in the kidney when the dose was above 2.5 cc. per kilo. The liability to formation of calcium oxalate crystals was greater when the ethylene glycol was given in divided doses.
3. Acutely toxic doses of ethylene glycol given to rats by mouth had no apparent effect upon the kidney and no crystalline deposits were found.
4. Long-time administrations of ethylene glycol and of ethylene glycol diacetate resulted in the deposition of calcium oxalate crystals in the kidneys of rats. One to 3 per cent. solutions caused the deposition of calcium oxalate crystals occasionally, but 5 per cent. solutions resulted in the more frequent deposition of large amounts of crystals and were rapidly fatal.
5. In no case did we observe hydropic degeneration of the kidneys of rats or rabbits from either ethylene glycol or ethylene glycol diacetate.
6. Young rats given one per cent. ethylene glycol in the drinking water were retarded in their growth, the mortality being about 50 per cent. during the 11 weeks of the experiment.

B. Experiments were performed to determine the effect of sodium oxalate on the kidneys of rabbits and rats.

1. The relative resistance of rabbits to single large doses of sodium oxalate or to smaller daily doses suggests that the cause of death from the intravenous solution of ethylene glycol is not alone due to the formation of oxalates or to an effect upon the kidney.
2. Sodium oxalate fed to rats in their drinking water in one or 2 per cent. solutions proved of low toxicity. Two per cent. solutions slightly retarded the growth of young rats. At no time was there observed any lesion in the kidney or any deposit of oxalate in the kidney tubules.

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COLLEGES IN A WORLD AT WAR AND IN A WORLD AT PEACE*

By Abraham A. Neuman, M. A., H. L. D.**

TO stand before young people and to address them in the hour of college graduation this year is an emotional, challenging experience. Certainly as I stand before you, I cannot help reflecting in my own mood some of the intellectual and emotional conflicts that are stirring the hearts of you, the graduates, and your fellows on the campuses throughout the country.

Students are dreamers and idealists at heart. Despite their apparent absorption in play and sports and their dread of appearing soft and sentimental, their secret passion is to create; their favorite pastime is to build Utopias; their cherished dream is to add to the sum total of truth and beauty which they found in this imperfect world. The creative impulse is the birthright of immortal youth. But this divine gift seems to be snatched from the grasp of the graduates of today. We are in the midst of global, total war. War maims and kills. It not only maims and takes many lives. It thwarts and distorts the very life impulse of youth. It turns its life-giving energies into death-dealing instruments. More dreadful even than the physical casualties which strike individuals is the shattering effect of war upon the hopes and ideals of the entire young fighting generation.

And yet fight we must. This is the dilemma of youth. We have not invited war. We hate it and all its works. War came upon us with tidal force from which there was no apparent escape. For the college youth, war sneaked upon them like a thief in the night. You young people were caught unawares. You were in your classroom when the treachery of Pearl Harbor was hatched. It is true that on the very day in September, 1939, when you matriculated as college

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freshmen, the Nazi dive-bombers shrieked over the ruins of Warsaw, and the piercing cry of the victims might have been heard round the world. But in those days, Poland was a terra incognita to most Americans and Guadalcanal was not in our geography. The mantle of isolation—that coat of many colors—then attracted all too many Americans, older in years and presumably wiser in experience, so that it was possible for one of the elder statesmen to laugh off the world tragedy as a "phony war." How the world has aged and changed for you these few years from September 1, 1939, through December 7, 1941, to this date in 1943, when you leave the shelter of the classroom, prepared to answer the summons of your country and to take your places on the global, totalitarian battlefield. It would be idle to imagine that your minds and your spirits are unaffected by the grim pattern which life has assumed.

Insofar as teachers are the interpreters of life, you have a right to look to your Alma Mater not merely for approval of past performance. The diplomas handed you this evening should be sealed with faith and illumined with hope. I like to look upon your diploma as a covenant, a covenant of faith which you and your Alma Mater mutually pledge each to the other. You vow fealty to truth, loyalty to the scientific and humanitarian ideals to which your Alma Mater is dedicated. Wherever your lot may be cast, whether it be in America or Europe, Asia or Africa, you undertake to uphold honorably the lofty traditions of this College in its pure devotion to the sciences of health. And I like to feel that in return, your Alma Mater offers you its pledge, in war and in peace, while unfurling the flag of our country, also to fly the banner of truth; to battle during the darkest hours of war for the right and the duty to pursue truth for its own sake; to push forward the frontiers of knowledge through research and investigation in the sciences which you have made your particular domain—the health sciences whose development holds out so much beneficence for the human race.

The moral compulsion of this covenant carries over deep into your personal lives and far into the future destiny of your College as a citadel of the human mind in the eternal quest for truth. For what do your diplomas testify? That you have severally acquired specialized knowledge in pharmacy, in chemistry, in biology, in bacteriology? That you have learned the technique of the practical application of your knowledge within the province of these vital disciplines? To

be sure, the world will so interpret it. But certainly your own perspective is not so restricted. More important than your grasp of what you know is your vision of the unknown. Higher in the scale of values than knowledge is the thirst for knowledge. Were God to stretch out two hands, the one holding truth and the other the search for it, the true scientist would forego the first and grasp the latter. The adventure of the mind is the glory of the human spirit.

Have you not personally experienced the intense excitement akin to the joy of a beautiful sunrise when you suddenly beheld the lifting of the mental horizon? Is there a student so poor in spirit who has not felt a singing of the heart, an upsurge of the spirit within, as his mind swept past its own beaten tracks and dared to challenge the mysterious, the unknown? Your diploma is infinitely more than a certificate of knowledge. It is an invitation to join in a great spiritual adventure. It will open to you secret doors where you may behold the company of immortals who mapped the world of thought. You will gaze at them and want to emulate them. Perhaps one or more of you may some day be admitted to that most select company. But all of you may rejoice in the fact that by your graduation today, you are being initiated into that most glamorous of all worlds, the world of science, which beckons to you alluringly, so full of adventure and endless discoveries. But, you ought to be cautioned, no one can truly make headway in that charmed world unless he keeps the covenant—the covenant symbolized in your diploma—the covenant, I repeat, with your Alma Mater and with truth itself, that you guard it sacredly, as you cherish the freedom of the mind and the dignity of the human spirit.

What then are your duties in this realistic world of war and extermination? It is not difficult to prescribe your immediate course of action. The call of country is strong and imperative. No American can ignore it and least of all the man of science. For him two worlds are at stake—this global, terrestial, physical world with its social, economic and political systems for the human inhabitants, upon which the elemental happiness of the human race depends, and secondly, the majestic world of the mind over which hovers the spirit of God and in which mystic tunes sing of truth, love and freedom even as in the Hebrew prophetic vision, angels intone:

"Holy, holy, holy is the Lord of Hosts, His glory fills the world."

The man who values the integrity of his soul will face a thousand

deaths rather than endure life in a disordered Nazified madhouse, where truth is a fetish, love a weakness and freedom a nostalgia of decadence.

As you are called into service, you will not shrink from any sacrifice in the line of duty. Because of the specialized training in the health sciences which you received in this College, you will be indispensable in various lifesaving services to which you will most likely be assigned. In this, you may consider yourselves extremely fortunate. Your opportunities will expand and not shrink when the order to cease firing will be heard and an armistice declared. You will then be in the front ranks of the soldiers of mercy who will continue the battle under the Stars and Stripes, this time against disease, famine and pestilence. You will bring healing, health and sanitation wherever you go. You will engage in the pioneer work of health engineering, so essential for the social reconstruction of conquered countries and ravaged nations. Your various tasks will help to pave the way for an orderly world of peace and international solidarity. This is a goal sufficient to thrill the heart of any young vibrant American endowed with imagination and imbued with the love of his fellowman. But in the daily performance of the military duties that lie ahead, you must guard against inevitable temptations and dangers. The regimented life of a soldier is not conducive to independent thinking; and yet the very breath of your young life as a scientist is spontaneity and freedom of thought. In a period of stress and strain, it is so tempting to fall into a mood of blind acceptance. Following orders is a soporific relief from the painful process of sustained thinking, but the result is mental deterioration. There can be no military efficiency without strict obedience; but neither are victories won by technical robots. In an ideological war, in a conflict between contending civilizations of freedom and slavery, the ultimate victory will fall not merely to the brave warrior but to the man who is brave enough to be free.

Keep the covenant and you will be free. Implicit in the covenant is the belief that God created you a thinking, sentient being; that to think, without chains or fetters, is the inalienable right of the soul. To this pact be true. Reverence of the mind is the beginning of science. To revere the mind is to keep it free—free from the weeds of prejudice, bigotry and hatred that choke thought. To revere the mind is to put it to use, consciously to set thought in motion actively, creatively, beneficently. To revere the mind is to scale the heights where

thought is free and truth compelling. A free mind is the shrine of the soul. It is the guardian of democracy.

Keep the faith for the day when the cruel winter of war's ravages will give way to the season of blossoming hope, and the time for planting the seed of a new world will be at hand. In that day, America will call for men of vision and integrity, for young men and women like you, trained to think, to work, to explore the avenues of science for new facts and new light. A world that well nigh destroyed itself had better give youth a bold share in the blue print of the new social order.

But youth must exhibit more than a deficiency of years. It must manifest courage, daring, discipline. It must be strong in faith, faith in its own integrity and power, firm in the conviction that divine reason fills the universe. Such a youth may reveal the invisible hands that with infinite love and compassion will bind the wounds of a stricken, bleeding world. Such a youth may with the discipline of science and the passion of love weave a world of freedom and peace out of the sighs and sorrows of suffering humanity.

To turn now from you, the graduates, to your Alma Mater, I take the liberty to underscore that the obligations of the covenant are mutual and reciprocal. The institutions of higher education must be conscious of the grave responsibility that rests upon them too, to keep the faith. When our warriors return from the battlefield, many of them prepared to resume their studies and to equip themselves for a decisive role in the new world, in what state will they find their colleges and universities? Today, all institutions of higher learning are on trial. Under the new conditions resulting from the law drafting boys, eighteen and nineteen years old, many of the colleges are about to abdicate their functions. This will become increasingly evident with the passing of the next semester. The education of college boys will be virtually taken out of the hands of the academic authorities, and will rest entirely with the military regime. Army officers will select the students, determine the curriculum and set the standards of academic life. Like many an industrial plant, great universities will soon be taken over in whole or in part by the armed forces and converted to war ends. Campuses will turn into camps, dormitories into barracks, while the muses and the humanities will be banished as intruders and interlopers. For the time being, the arts, literature, philosophy and history will be relegated to the mental scrap

heap. The classics must give way to the study of mere languages. The dialects of North Africa and the Malayan jungles are already enjoying priority over the languages of Plato and Cicero. The army concepts of education will hold sway: science—streamlined—for technology—reading and writing for commands.

It will be argued that these are the dire necessities of war. But are they? No one will for a moment dispute that when a nation fights for its life, no sacrifice can be considered too great if it is in the interest of winning the war. But will the war effort gain if in the critical years that are now at hand the idealism and the brains of the student youth will be narrowly channeled through a military funnel? Is this indeed the considered opinion of scholars and educators, or is it being foisted upon the academic world as a military fiat, unilaterally, without even the meeting of minds on essential principles? Thinking Americans who look to the academicians as the true guardians of civilization want the truth and want it in accents bold and clear. Is there to be a moratorium on liberal education for the duration of the war? Are the students graduating this month from the colleges throughout the country the last of their fellows to receive a full collegiate training until the holocaust is over? Is there to be a hiatus in the ranks of college-bred Americans? Must America face the dilemma of inaugurating the greatest task of social reconstruction known in history under the handicap of such a heavy toll of potentially trained personnel?

Labor makes known its demands with strident voice. The farmers have their bloc in Congress. Have the universities and colleges no viewpoint to press upon the nation? When the foundations of higher education are threatened, who shall sound the alarm but they whose duty it is to guard the ramparts of civilization? Theirs would not be the voice of vested interest or privilege, but the voice raised in defense of the nation's highest resources, the accumulated wisdom of the ages.

We want to view the dilemma of our academic brethren with sympathetic understanding. All of us are impelled by an ardent desire to serve our country. The nation's war needs are paramount in our thoughts. We feel uneasy and restless if we do not have a direct personal share in the war effort. Some of our colleagues have been singled out for vital war service. Many others, however, have forsaken important academic posts in order to be attached even in a

minor capacity to some form of war effort. As long as this is the dominant psychology in the academies of learning, what hope is there for the kingdom of the mind?

The university no less than the Church has a philosophy—an invisible kingdom—to defend and maintain. Through centuries of trial and martyrdom, the Church at its best has learned the painful art of being true to itself and keeping faith with the world. Witness the glorious defiance of despotism by the Church in Nazidom. In a free democracy, the Church places all its powers at the service of the State, but it does not surrender its own spritual autonomy. Let the universities learn this precious lesson from the Church. When the State trespasses upon the kingdom of the soul, the Church cries aloud. When force threatens the realm of the mind, let its guardians stand up and be heard. These are heresies to be resisted for the sanctity of reason no less than for the salvation of the soul. It is heresy to believe that mere technical training is education. For responsible authorities to foster this thought even in wartime is to encourage a dangerous fallacy in the days to come. It is heresy to believe that a nation can without peril to its future dispense with humanistic culture or abstract thought even for the duration, for as the modern sage behind the taxi steering wheel remarked: "It looks to me as if the duration will last longer than the war!"

Our institutions of learning must not through timidity or through confusion of loyalties fail civilization in the hour of its direst need. It is dark enough without educational blackouts and mental dimouts. When the world was in chaos and unformed, God said, "Let there be light." And when society, thrown back into primeval chaos seeks to reorder its life and, bleeding from a thousand wounds, cries for a new era of peace, freedom, light, whence shall light come if not from those who have from time immemorial carried the banners of truth, and held high the flaming torch of thought and freedom? This is not a time for men of learning to be self-deprecating, paralyzed with caviling doubts about the value of culture in a war of jungles. There are weapons of war for the jungles; but we must also have tools of the mind to clear the jungles and banish war forever. Let men of learning take heart for freedom's sake. Through as many disciples as they can muster and by their own lives they shall bear witness to the power of ideas and ideals. This is their destiny: in a dark world to feed the flames of thought and ideals; and in the brighter day to lead man-

kind through knowledge to the ways of truth, peace and abundance. Will the covenant be kept? We shall not be held guilty of overstatement if we say that with the answer are bound up the hopes and aspirations of mankind.

My thesis is stated. The covenant is before you. The challenge, I trust, will be accepted by men high in academic leadership. I can not help adding, however, a personal word. I am glad that Doctor Griffith gave me the opportunity to voice my thoughts from the platform of the Philadelphia College of Pharmacy and Science. It is my opinion that to an important degree, hope for the future rests with the smaller institutions, where devotion, research and independence of thought are personalized and the faith of students is kindled by the precepts and the example of the master mind.

The history of your College gives striking confirmation of the covenant relationship between an institution of learning and the progress of a nation. The founders of this institution did not follow any formal preconceived educational pattern. Quite the contrary. They rebelled in no uncertain terms against what they felt to be the unwarranted assumption of authority over their profession by a great university. They were rebels because they had the courage of faith. They had faith in their own integrity and faith in the unlimited possibilities of the pharmaceutical sciences. In this faith they founded the College and gave an impetus to the growth and evolution of a profession which has profoundly affected the welfare of the American people.

It is not surprising, therefore, that as the College grew, the horizon of pharmacy was expanded. Thus, decade after decade, there was a marked parallel between the expansion of your institution and the evolution of the sciences which you have increasingly brought within the program of your studies and researches. Your growth from a college of pharmacy to a college which embraces the various sciences of health was not merely a physical-mathematical process of addition and multiplication. It represented organic evolution. It was the reaction of science to life. Therein lies the inspiration which your history of a century and a score of years holds for the perplexed generation of our time. Your College was born of American faith and courage: faith in original research and study; faith in man, endowed by the Creator with the power of mind and reason; faith in the unlimited possibilities of knowledge to affect the welfare of mankind; and courage to put that faith to the test with vision and sacrifice.

Succeeding generations of boards and faculties, students and alumni, have kept that faith. With a proud record of scientific achievement, an inspiring roster of pioneers and brilliant scientists connected with your College, you, the leaders of today, can be trusted to bring to the complicated problems of the future, high courage, vision and faith. For this is your covenant and you will keep faith.

In conclusion, you will grant me, I hope, a word *pro domo mea.* Is it not symbolic that you have chosen as the speaker for this unusual occasion, combining Commencement and Founder's Day, one who represents the humanities and, furthermore, a branch of studies that superficially, at least, bears no direct relationship to the sciences which are your domain? It happens that Moses Aaron Dropsie, founder of the College for Hebrew and Cognate Learning, which bears his name, was born in Philadelphia in 1821, the year when your College was founded. But I can hardly ascribe my appearance on your platform to such an esoteric reason. I want to feel that consciously or subconsciously, perhaps, you and I are thus expressing a joint conviction about the universality of the kingdom of the mind.

Our studies at Dropsie College, postgraduate in character, nonsectarian and non-theological in content, carry us back to Bible and pre-biblical days. We explore the languages and civilizations of Egypt and Babylon, Palestine and Syria. We study the remains of ancient civilizations, the mathematics of Babylon, the sciences of Egypt. We seek through intensive study of the Bible and the Talmud better to understand the nature of the Hebrew genius in religion and ethics and the profound influence exerted by little Palestine upon the destiny of the human race.

Do these subjects seem remote to you, men of the laboratory and the microscope? Truth is visible at both ends, the finite and the infinite. Nature reveals its secrets through the telescope as well as the microscope. The deeper we probe the mystery of nature, the clearer we find the imprints of the unity and continuity of truth. In Germany, the realization has led to an assault on truth on all fronts—science, religion, history, art and literature. It is a glorious symbol, therefore, that we on the platform of this American College, by our presence and by our words, attest our faith in the unbroken and invincible power of truth. They who battle for truth on the battlefield, in the laboratory, in the recesses of the mind, are allies in spirit and in fact. With truth to defend, victory is assured. The trophy will be freedom.

COSMETICS TODAY

By T. Swann Harding*

HOW have cosmetics fared under the new laws enacted not so long ago which placed the regulation of labels under the Food and Drug Administration, in the Federal Security Agency, and of advertisements under the Federal Trade Commission? Is the market still filled with dangerous cosmetics? Were very many dangerous ones found and run off the market?

For a good many years cosmetic advertising was essentially a contest in competitive prevarication. The most extraordinary claims were made for cosmetics, many of them so incredible that consumers lost all faith in them and even the advertising agents found difficulty in believing them. There were sharp calls for government regulation from within the industry.

Gradually, as scientific research advanced, there arose a natural tendency to load cosmetics with medicinal agents such as vitamins, hormones, androgens, estrogens, and so on. Now it is true not only that the fats and oils in cosmetics can be absorbed through the skin but also that drugs can be so absorbed. The rate of absorption is influenced by the nature of the drug and the vehicle.

Thus volatile substances like alcohol, ether, and benzine cause a higher absorption rate than do fats. But fats can permeate the skin along the hair shafts and by means of the oil-ducts, liquid fat penetrating more quickly than solid, animal fats penetrating deepest, vegetable fats next, mineral oils least. Most fats penetrate as much as they ever will from four to six hours after application. After six hours the quantity in the deeper tissues tends to diminish.

That is natural. For fats rubbed in through the skin eventually enter the blood and lymph streams and proceed to nourish the body quite as if they had been eaten—only eating is a more rational and efficient way to absorb them. As for drugs—though it is possible to dose yourself by rubbing drugs through your pores, it is both more

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sensible and more scientific to take known doses of drugs by mouth or have them injected by a physician, than to depend on skin absorption. In the latter case dosage cannot be controlled and untoward results may follow.

Cosmetics therefore should not contain ingredients capable of producing constitutional effects. They should not contain poisons like mercury, arsenic, or thallium acetate, and they rarely have in recent years. But the manufacture and sale of therapeutic and medicinal cosmetics of any kind constitutes a menace to normal people. The complete formula should also be placed on all cosmetics as an aid to the allergic.

Cosmetics do have some value as protective and cleansing agents and as lubricants. Today there are few if any dangerous creams or lotions left on the market. Most of the creams containing mercury have in recent years aroused suspicion by being recommended as bleaches, while those highly dangerous ones containing thallium acetate were advertised as removers of excess hair. One of the latter was responsible for some fatalities a few years ago. In general, ordinary face and body creams and plain lotions, recommended as such, have been safe.

Good soap and water will form quite as effective a cleansing agent as a cream and now that soap making is scientifically carried on few soaps have ill effects. The chemical effects of cold creams are rarely bad, however. Bleaching preparations, freckle and blemish removers, and most hair dyes and depilatories should be avoided by laymen. Anti-perspirants and deodorants are usually harmless if selected with care. Dentifrices do aid in cleansing the teeth and mouthwashes make good oral cosmetics without effective medicinal action. The field of preparations for the hair, eyebrows, eyelashes, and nails is limited.

Nevertheless, according to the Census Bureau, consumer expenditures in a normal year for goods and services to enhance beauty amount to $800 millions. Women spend about $16 each a year for beauty aids as compared with the $77.20 per capita we spend in food stores and the $21.44 pre-war spending in filling stations. In 1940 there were 83,071 beauty parlors doing an annual business of $231 millions, and 539 plants making cosmetics, perfumes, and toilet preparations with an annual factory value of $147 millions.

The beauty industry employed about 150,000 all told. The wholesale write-up on cosmetics is usually 40 and the retail write-up

another 35 per cent. The factory value of creams, not including shaving creams, was $20 millions in 1940, that of face powders over $15 millions, perfumes nearly $9 millions, toilet waters nearly $8 millions, face lotions about $8 millions, talcum powders nearly $7½ millions, hair dressings about $7 millions, lipstick and lip rouge about $6 millions, manicure preparations and shampoos approximately $4½ millions each. That gives an idea of the financial extent of this industry in which the exigencies of war are making drastic changes.

When Federal intervention came in the cosmetic field it took the form of the Food, Drug and Cosmetic Act which was passed in 1938 and went fully into effect in 1940. In 1938 also the Wheeler-Lea Amendment to the Federal Trade Commission's organic act was signed by the President. The former gave to the Food and Drug Administration jurisdiction over container size and labeling of cosmetics; the latter gave to the Federal Trade Commission power to forbid false and misleading advertising claims as a form of unfair competition in trade.

Both laws also related to other products. The two agencies have worked in close harmony in enforcing the laws. There has even been some interchange of personnel. Their attitudes towards label and advertising statements agree closely. However, the Food, Drug and Cosmetic Act is more strongly worded than the Wheeler-Lea Amendment.

The former states: "A cosmetic shall be deemed misbranded if its labeling is false or misleading in any particular." The latter, however, says that: "The term 'false advertisement' means an advertisement, other than labeling, which is misleading in a material respect." It is more difficult to prove that a statement is false and misleading in a material respect than that it is simply false and misleading.

Soaps are exempted from the Food, Drug and Cosmetic Act which defines a cosmetic thus: "The term 'cosmetic' means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles." The definition is broad and would include preparations for the face, scalp, hair, and nails, as well as dentifrices, mouthwashes, perfumes, reducing agents, products to combat body odor, or even clothes for that matter.

By examining the label claims upon which the Food and Drug Administration took action we can find out how cosmetics lined up. On August 2, 1939, a statement was issued to the trade notifying producers that the following claims would henceforth be regarded as false and misleading:

> "Contour cream; crow's-foot cream; deep-pore cleanser; depilatory for permanent removal of hair, in case it only bleached the hair; eyelash grower; eye-wrinkle cream; hair color restorer; hair grower; hair restorer; nail grower; nonallergic; peroxide cream; rejuvenating cream; scalp food; circulation cream; enlarged-pore preparation; hair-revitalizing preparation; muscle oil; nourishing cream; pore paste; skin conditioner; skin firm; skin food; skin-texture preparation; skin tonic; stimulating cream; tissue cream; wrinkle eradicator; any cosmetic represented as of value because of its vitamin content."

A reading of that list will pretty well inform you about false claims. In the same notice, addressed to manufacturers, packers, and distributors, it was explained that a number of preparations had been found misbranded because they were represented as containing ingredients not actually present, or present in negligible quantity. The notice also stated that designation of a product by the name of one, exclusive ingredient, would not be permitted.

Under this law a cosmetic is also deemed adulterated if it contains a poisonous or deleterious ingredient which may render it injurious to the user; if it consists in whole or in part of any filthy, putrid, or decomposed substance; if it has been packed or prepared or held under insanitary conditions; if its container is composed in whole or in part of any poisonous or deleterious substance which may render it unhealthful; or if it contains a coal-tar color which has not been certified for such use by the government. Containers so made or formed or filled as to be misleading are also illegal. Informative labeling required by the law must be printed conspicuously.

On November 8, 1938, manufacturers of eyebrow and eyelash dyes were warned against using paraphenylenediamine or paratoluylenediamine in these preparations. On May 13, 1939, manufacturers were told that mercury bleach creams containing more than two-tenths of a per cent. of mercury bichloride, or comparable quantities of other mercury compounds, would be subject to immediate action under the law.

On October 17, 1939, an order was issued that coal-tar dyes which might be injurious to users required precautionary labels, the

form of which was given in full. These warned users not to apply the preparation to the eyelashes or eyebrows, and to apply it to the hair of the head only after making patch tests on the skin as per instructions also given. The precautionary statement must appear on labels in a color of print contrasting with the background and with that of other printed matter on the label.

Immediately the new law went into effect an onslaught was made on harmful cosmetics. They were speedily cleared from the market. The report of the Chief of the Food and Drug Administration for 1940 says that this campaign began three weeks after the law went into effect, 85 seizures were made and 49 criminal prosecutions were instituted. Special watch was then put on products which might change their recommendations, but most manufacturers quickly changed formulas or withdrew their products from interstate commerce.

The Food and Drug Administration periodically issues what are called Notices of Judgment which briefly abstract actions it has taken. A list issued May 1940 stated that action had been taken against the following for containing paraphenylenediamine: Lash Lure, Magic-Di-Stik, Loris Permanent Lash and Brow Colure, Hollywood Lash and Brow Dye, Mary Luckie Improved Lash and Brow Dye, Ideal Lash and Brow Dye, Andree Eye Lash and Brow Colure. These were all for the eyelashes and brows. Another product of this sort, Dark Eyes, was proceeded against because it contained ammoniated silver nitrate and pyrogallol.

The following hair dyes were seized because they contained paraphenylenediamine: Eau Sublime Hair Coloring, Madam Marva Hair Coloring, and Posner's Black Hair Coloring. Action was taken against Guerlain Lipsticks because they contained cadmium and selenium, against Madam C. J. Walker's Tan-Off and the skin bleach, Othine, because they contained ammoniated mercury, against Miller's Anti-Mole for containing nitric and acetic acids, and against the following for containing mercury bichloride: O. J.'s Beauty Lotion, Palmer's Antiseptic Skin Lotion, Soule's External Lotion.

The following are cited in the same notices as misbranded because their containers were deceptive: Sears Tooth Paste, Walter's Toothpaste, Cabot's Toothpaste and Milk of Magnesia, Lee's Milk of Magnesia Dental Cream, Gibson Milk of Magnesia Dental Cream, Gibson Howell Shaving Cream, Hush Cream Deodorant, Hush-Sno, Yodora Deodorant Cream, Evening in Paris Face Powder, Max Fac-

tor's Face Powder, and powders called White Swan and Sweet Pea. Notices published January 1942 cited Jasmine Dusting Powder and Philips Milk of Magnesia Cleansing Cream for deceptively filled containers.

Further notices published May 1941, cited actions against Andree Permanent Eye Lash and Brow Culture for containing paraphenylenediamine; Louise Norris Lash and Brow Coloring for containing 2,5 toluylenediamine which was not from a certified batch: and against Farr's For Gray Hair for containing silver nitrate and diamidophenol hydrochloride, as well as for not bearing the legally required precautions on the label.

At the same time action was announced against L. B. Hair Oil for false and misleading label misrepresentations as a scalp remedy, a preventive of baldness, a remedy for granulated eyelids, and an eyelash growth stimulant. This same product was mentioned again for the same reasons in a further notice issued November 4, 1941—and also for deceptive packaging.

The following have been held misbranded because their containers were deceptive: Blue Ribbon Dental Cream, Comfort Manufacturing Company's toothpaste, Gotham Sales Co.'s Milk of Magnesia Dental Cream, Iodent Tooth Paste, Kolynos Dental Cream, Laymon's Tooth Paste, Pebeco Tooth Paste, Gibson's Tooth Paste, Colgate Ribbon Dental Cream and liquid, Listerine Shaving Cream and Tooth Paste, Seven Star Brushless Shaving Cream, Neet Cream Hair Remover, Zip Depilatory Cream, Kurlene Eyelash Cream, Fresh No. 1 Deodorant, and No. 2 Non-Perspirant Vanishing Cream.

Finally Odell's Quinine for the Hair was cited for containing no quinine, for not bearing on labels the names of its ingredients, and for making the claim "essential to healthy hair." Miracle Lotion was acted against for false and misleading label statements as to its efficacy. Its claims to remedy scalp disease, dandruff, pimples, falling hair, body itch and so on were declared false. La-Nu Hair and Scalp Vitalizer was misrepresented somewhat similarly.

As can be seen many of these actions were taken against little known products of no great sales volume; those taken against nationally known products sold in large quantity in the main concerned infractions of the law which did not menace health. Meanwhile the actions of the Federal Trade Commission have in general curbed the exuberant mendacity of cosmetic advertising claims, such as forbidding soap manufacturers to claim that their product was

beneficial because of its vitamin D content, its extreme purity, or its egg ingredient.

Soap makers who insisted that their soaps were made only of olive oil, hence would keep the skin smooth and alluring, render it young, nourish it, or improve it 100 per cent. were compelled to make a strategic retreat to the truth. Makers of creams and lotions were forbidden to claim beneficial effects because their products contained certain vitamins, hormones, or turtle oil.

Other false claims for creams were such as: Erases skin blemishes; kills germs; penetrates deeply into the tissues; nourishes the skin; is beneficial for *both* oily and dry skins; removes wrinkles; cleans all dirt and debris out of the pores; eradicates blackheads and lines; lifts facial muscles; helps facial contour; releases oxygen for the skin to absorb; restores the skin's "natural youth glands." False claims for irradiation were also forbidden.

Manufacturers of milk of magnesia creams were told not to claim that these overcame "acid" skin just as magnesia used as a cathartic remedies bodily "acidity." For milk of magnesia has no therapeutic effect in treating skin blemishes, enlarged pores, fatty acid accumulations; it will not penetrate and cleanse the pores or improve skin texture; there is no such entity as "acid skin" anyway.

Still other claims forbidden as false run thus: Feeds or nourishes the skin and/or lips; restores youth to the skin; prevents crow's feet and/or wrinkles; contains "living sparks of life"—hormones to you; slenderizing bath salts which dissolve fatty tissue; eye lotion to relieve eyestrain and strengthen the eye nerves; promotes the growth of eyelashes; "youthifying" herbal mask; pre-expanded particles in a balsamized face powder which therefore would prevent enlarged pores and was moistureproof.

That about completes the docket. The really dangerous cosmetic is now rare. Properly performed patch tests readily aid the allergic, for allergy and special sensitivity remain. Thus there was the case reported in April 1941 of a woman who died as a result of undergoing a cold-wave process for hair waving (the Willat Method of Heatless Permanent Waving). This took place in a beauty shop. The product used was a water solution of ammonium hydrogen sulfide which had been tried repeatedly by the inventor of the process on himself and widely used over the country. Yet in this instance a fatality occurred.

Such unfortunate accidents are unavoidable so long as hypersensitivity exists in certain individuals. In this case the wave solu-

tion was seized in five hundred beauty shops, but no other recorded fatality or injury from its use could be traced down. (See Notices of Judgment published January 1942.) Not even toxicologists had hitherto recognized this source of danger to human life. Designation of a product as nonpoisonous simply means that it is not toxic to the vast majority of physically normal people. But disclosure of full formulas on all cosmetics would be of much help to consumers and would doubtless not injure business at all.

In summary: Really dangerous cosmetics have just about wholly disappeared from the market. Labels and advertising are more honest than they have been for years. Manufacturers quite generally strive to conform to the law. As nearly as can be expected the average person is today fully protected from harm when she purchases a cosmetic though she may still believe that the product will do more for her than it actually can.

What the war will do to the cosmetic business no one certainly knows today but plenty is expected. However, even under blitz conditions the British have found it possible and useful to continue the manufacture of some cosmetics for domestic use. Advertising has been curtailed and all the separate companies have been merged for the war period. A very few large plants make all the cosmetics though the products continue to appear under their familiar individual labels. Something of the sort, though doubtless to a lesser degree, will certainly happen here in time.

However milady is determined to look as beautiful as she can, she is under the carefully cultivated and cherished illusion that cosmetics abet the hand of Providence in this matter of creating beauty —and there you are.

BOOK REVIEWS

Cloves, Oil of Cloves, and Eugenol; Their Medico-Dental History. By Eugene J. Molnar, M. D., D. D. S. Research Associate, Northwestern University Dental School, Toledo, Ohio. Reprints from Dental Items of Interest, 1942. 30 pages. Illustrations.

This is a very complete monograph on its subject and was written with the thought in mind that the history of an old drug gives one an idea of the evolution of drug therapy, especially in that branch of medicine in which the drug is used.

Oil of Cloves is a valuable drug in dentistry for the relief of pain. Its exact pharmacologic qualification for the treatment of caries and odontalgia has been studied but still remains controversial.

The action of eugenol in ZnO-rosin cements, which forms our best temporary filling materials, also remains unknown.

Included in the article is a very extensive bibliography on this subject. M. O. H.

Drug Products: Labeling, Packaging, Regulation. By Arthur Donald Herrick, Member of the New York and Federal Bar. 462 pages, including index. Revere Publishing Co., New York. Price: $7.50.

The passage of the Federal Food, Drug and Cosmetic Act in 1936 led to a condition extending for several years which was most difficult. A plethora of situations arose needing clarification and it was not to be unexpected that some confusion would result. Time, however, cures all ills and now a fairly reasonable and systematic discussion and outline of the numerous regulations is possible. The author has prepared this text chiefly for the purpose of assisting the average manufacturer or distributor of drug products and cosmetics to understand and apply the statutory requirements pertaining to his particular business.

The book is divided into twenty chapters dealing with every phase of the subject from the developments leading to the Act, to the

Act itself and its many provisions. There is also a rather extensive appendix including amendments, methods of testing, case reports, etc.

It is obvious that there can be no book covering every conceivable point that might arise in such a wide field but a great deal of assistance is given to those who wish to study their problems in the light of what precedents are established and what requirements are to be expected in any given case. Although this reviewer is not a legal expert, the book seems well organized and clearly presented and it deserves the attention of the industry. L. F. TICE.

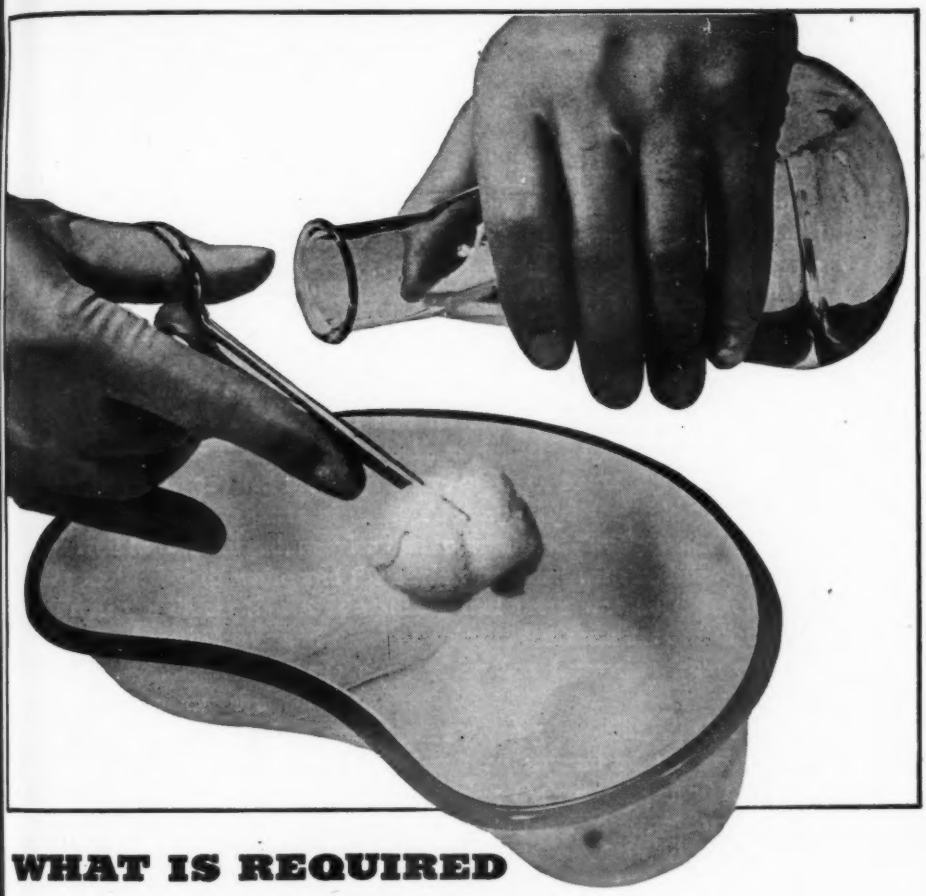
Check List of Native and Introduced Drug Plants in the United States. By E. N. Gathercoal, with the collaboration of H. W. Youngken, under the auspices of the Committee on Pharmaceutical Botany and Pharmacognosy of the Division of Biology and Agriculture of the National Research Council. Chicago, 1943. Price: $0.75.

This check list is designed as an aid to botanists for checking the drug plants found growing within the individual states of the United States, but not including the insular possessions in the West Indies and distant Pacific.

All of the botanical items ever recognized in the United States Pharmacopœia or the National Formulary have been included along with fifty-three unofficial items. In this manner three lists were formed, namely: (1) The Check List (true) of Native and Introduced Drug Plants in the United States; (2) a list of Foreign Medicinal Plants that are seldom or never cultivated in the United States; and (3) a group of thirty-five drug plants that were recognized at one time in the U. S. P. but now are not even listed in the botanical catalogs. This list is included simply to present the complete number of botanical items ever recognized in the U. S. Pharmacopœia.

In the introduction there is presented a number of limitations which were observed in making up the list. The physical form of the check list includes drugs arranged alphabetically according to the botanical name, followed by the drug derived from that plant, and the official location.

The check list should be of definite value to those interested in this field. M. O. H.



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